REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

The Official Action asserts that "[n]ewly submitted claims 21, 23, 25, 27 are directed to an invention that is independent or distinct from the invention originally claimed." Page 2. A method of treatment of chronic heart failure was said to be independent and distinct from treatment of cardiac hypertrophy. This assertion is in error.

Claim 21 was *not* newly submitted in the July 2, 2001, Amendment. In that Amendment claims 23, 25 and 27 were newly presented. However, claim 21 was previously submitted in the Amendment dated October 24, 2000. This claim had been examined together with claims 6 and 8-14, as shown in the Official Action dated January 2, 2001. Moreover, claim 7 was presented in the Preliminary Amendment submitted with the application as originally filed. This claim recited that the heart disease based on cardiac hypertrophy is chronic heart failure. This claim was examined and considered, as shown by the Official Action dated April 26, 2000. Claim 7 was rewritten as an independent claim in claim 21. Applicants thus never made a "constructive election" of cardiac hypertrophy versus heart failure. Since claim 21, as well as original claim 7, directed to treatment of chronic heart failure was already considered and examined by the Examiner, and a prior art search directed to this subject matter was presumably already made, it is improper to now withdraw this claim, and claims dependent therefrom, from consideration.

Withdrawal of these claims is thus believed to be in error. Reconsideration is thus respectfully requested.

Claims 12-14 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be moot in view of the instant amendment.

Claims 12-14 have been rewritten as new claims 28-29. These claims do not depend from claim 6. These claims are directed to continuous administration, using different forms of administration - oral, intravenous, intramuscular and subcutaneous - and various delivery forms. While the Examples cited for support of "continuous" administration are directed to continuous "intravenous" administration, it is respectfully believed that one skilled in the art would not read "continuous" so narrowly as including only "intravenous" administration. One skilled in the art would recognize that other forms of continuous administration are employed in the art. Before the Patent Office, claims must be given their "broadest reasonable interpretation." *In re Zletz*, 893 F.2d 319, 321, 13 U.S.P.Q.2d 1320, 1322 (Fed. Cir. 1989). Limitations may not be read into the claims from the specification. "That the claims are interpreted in light of the specification does not mean that everything in the specification must be read into all the claims." *Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592, 597 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984). Giving "continuous administration" its "broadest reasonable interpretation," one skilled in the art would not read it as encompassing only intravenous administration.

Withdrawal of the rejection is thus respectfully requested and believed to be in order.

Claims 6, 22 and claims dependent therefrom have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be rendered moot by the instant amendment.

The Examiner asserts that it is not clear whether the phrase "not based on diuretic and hypotensive effects" relates to the heart weight, cardiac hypertrophy or to a method of treatment of the latter. The phrase "amount ... not effective for said diuretic and hypotensive effects" is also alleged to not be clear. This phrase relates to the heart weight, and the reduction thereof is "not based on diuretic and hypotensive effects." The claims have been amended to make this more clear by reciting "wherein said reduction of heart weight is not based on diuretic and hypotensive effects" and that "said amount is not effective for said diuretic and hypotensive effects."

Withdrawal of this rejection is respectfully requested and believed to be in order.

The Official Action further discusses the dosage calculations presented in applicants' prior response at pages 4-6 of the Official Action, and disagrees in part with the conclusions reached. Applicants address these discussions as follows.

On page 5, lines 3-6 of the Official Action, it is asserted that Example 1 describes preventing cardiac hypertrophy rather than treating the already developed disorder. While Example 1 shows the effect of preventing cardiac hypertrophy at pressure overload, Example 2 of the application shows the effect of treating cardiac hypertrophy after it has occurred. In both examples, ANP at a dose of 0.1 μg/kg/min was shown to reduce heart weight. The blood ANP levels at that time were 502 pg/ml and 426 pg/ml, respectively.

Based upon these studies, applicants believed that the maintenance of blood ANP levels at about 0.5 ng/ml would be effective for both preventing and treating cardiac hypertrophy.[1]

The Official Action further asserts that the level of 0.5 ng/ml is limited for a particular time point and that Hayashi shows that ANP blood levels are not stable in time. This assertion is also disputed.

Since ANP is being given by constant intravenous infusion, it is reasonable to believe that the blood levels during the administration period are constant (*see,* Figure 4 in Hayashi et al and Figure 6 in Obata et al). Since Figure 6 in Hayashi et al is not the result of a continuous intravenous administration, but of rapid intravenous administration, it is only natural that the levels vary with time. Please also note Table 2 of Hayashi et al. Css at the time of administration of 0.1 μg/kg/min is 0.6 ng/ml, which is essentially the same as applicants' data, showing 0.5 ng/ml. Contrary to the assertion in the Official Action, there is no gender difference described in Hayashi et al. ANP is known to be metabolized via clearance receptors and neutral endopeptidase, and not via hepatic p450 (for which a gender difference often becomes an issue). Thus, no gender difference is recognized.

On the bottom of page 5, the Maeda reference is objected to as being published after the filing date of the instant application. The Official Action further states that Maeda shows that the levels of BNP are different from ANP. This assertion is disputed as BNP is mentioned in the article with reference to the variation of endogenous BNP. This is entirely different from the variation of ANP levels that were externally administered.

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[1]The difference of 502 and 426 ng/ml is not significant. What is important is that the level be such that diuretic and hypotensive effects do not appear.

Additional references that were available in the art as of the filing date of the instant application are submitted herewith to show extrapolation of dosages from rats to humans. These references are as follows:

Adnot et al, *J. Clin. Invest.* 83:986-93 (1989)

In this article, patients with COPD received a continuous intravenous infusion of ANP at 0.01-0.1 μg/kg/min, and blood levels and hemodynamics were determined. The results were as follows: (1) within this dosage range, blood ANP levels increased in an almost linear manner (Abstract); (2) blood pressure decreased only at 0.1 μg/kg/min (p. 988, upper right-hand column); (3) the basal ANP level was 136 pg/ml (Table IV); (4) ANP levels during the ANP administration period after subtracting the basal level are 182 pg/ml at 0.01 μg/kg/min, 1187 pg/ml at 0.03 μg/kg/min and 3453 pg/ml at 0.1 μg/kg/min (Table IV). From each of these values, blood ANP levels can be determined at the administration of ANP 0.025 μg/kg/min by a linear equation to be 580, 989 and 863 pg/ml. The hypotensive effect appeared at 0.1 μg/kg/min.

Kakuo, *The Clinical Report* 27:1549-65 (1993)

This article shows the result of a clinical Phase I trial of human ANP. Table 8 (page 1563) shows blood levels obtained during continuous intravenous infusion of ANP at 0.1 and 0.2 μg/kg/min, in which ANP levels become 1599 and 3829 pg/ml after subtracting the basal ANP level (21 pg/ml), and hence, there is an almost linear relationship between the two dosages. From these levels, the blood level during the administration of 0.025 μg/kg/min would be calculated to be 400 and 491 pg/ml with the

mean value being 446 pg/ml. This value is almost identical to the value obtained by applicants when 0.1 μg/kg/min of ANP was given to rats.

Obata et al, *Jpn. Pharma. Ther.* 21:1103-14 (1993)

This article studied blood levels and pharmacological effect during the continuous intravenous infusion of 0.1 μg/kg/min of ANP to patients with acute cardiac failure. The basal ANP level in the patients was 283 pg/ml (p. 1109, left column) and Css [steady-state concentration] during the administration was 2120 pg/ml (1837 pg/ml after subtracting the basal level). Since there appears to be a linear relationship in the blood levels between the administration of 0.025 μg/kg/min and the administration of 0.1 μg/kg/min, the level when 0.025 μg/kg/min was administered can be calculated by a linear equation to become 489 pg/ml. This value is in keeping with applicants' results.

From the foregoing, it can be seen that the blood level of ANP when 0.025 μg/kg/min was administered is 811 pg/ml in Adnot et al, 446 pg/ml in Kakuo, and 489 pg/ml in Obata et al. The mean value of these three is 582 pg/ml, which is similar to the level obtained when 0.1 μg/kg/min ANP was administered to rats. Thus, the dosage in humans can be predicted based on data from rats. Furthermore, the fact that major changes in hemodynamics were not observed during the administration of ANP at 0.025 μg/kg/min is also described in an article by Sugimoto et al, *Jpn. Pharmacol. Ther.* 21:1083 (1993), which describes the results of a clinical phase 2 trial on HANP).

In view of the above, applicants' calculations were proper.

Claims 6, 8-14 and 22-24 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described by the specification. This rejection is respectfully traversed.

According to the Examiner, the phrase "amount ... not effective for said diuretic and hypotensive effects" does not have support in the specification. The Official Action asserts that the lack of diuretic and hypotensive effects during treatment of cardiac hypertrophy is not shown since it is only shown for prevention. Applicants, however, have found that neither diuretic nor hypotensive effects resulted during treatment or prevention of cardiac hypertrophy according to the instant invention. The lack of adverse effects are shown in Example 2 of the application. In a hypertensive cardiac hypertrophy model (aortic stenosis), no diuretic effects appeared during the one-week period of ANP administration, and the formation of cardiac hypertrophy was inhibited/prevented though there were no changes in blood pressure at the completion of the administration. Further, at the same dosage (and about the same ANP blood level), ANP treats an already formed cardiac hypertrophy (reduces heart weight), and thereby have expressly indicated "the effect of treating cardiac hypertrophy by ANP." The absence of hypotensive effects has also been confirmed at the completion of administration (that is, the middle of administration since the administration has not been stopped).

It is further asserted that since the secretion of ANP and BNP increases with the formation of cardiac hypertrophy, the prevention and treatment thereof are entirely different. However, as discussed *supra*, ANP exhibits effectiveness at the same dose for both prevention and treatment. It is within this range that diuretic and hypotensive effects

do not appear, and the endogenous level is insufficient to inhibit cardiac hypertrophy though the secretion of ANP and BNP increases compensatorily depending on the degree of load to the heart during the pathological states considering that in a mode (800 pg/ml) in which blood levels of endogenous ANP markedly increase as in the volume overload model (ateriorvenous shunt model, Example 3), the same dose and the same blood levels were effective. The "insufficient" ANP level is not greatly different in the onset and the forming period of cardiac hypertrophy, or not greatly different with the factors that induce cardiac hypertrophy, which expressly indicates that cardiac hypertrophy can be inhibited or involuted by externally supplying this level (equivalent to about 500 pg/ml in this result).

The statement in the Official Action suggests that where endogenous ANP is high, a higher dose of ANP is naturally required. However, that is not the case. Applicants surprisingly found that a statistically significant effect was obtained at the same dose of ANP. It is true that the preventive effect and the therapeutic effect are often different, i.e., an agent that exhibited a preventive effect cannot be considered to always be therapeutically effective (e.g., α1-blocker). Applicants thus found for the first time that ANP not only prevents cardiac hypertrophy, but also treats, i.e., involutes it.

In view of the above, withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claims 22, 24 and 26 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. This rejection is respectfully traversed.

The Examiner asserts that the phrase "amount sufficient to achieve a plasma level of about 0.5 ng/ml" during treatment of cardiac hypertrophy is not supported and is new matter. While Example 1 has ANP levels of 0.5 ng/ml or lower for prevention of cardiac hypertrophy, the same blood levels of 0.5 ng/ml or lower are also shown for prevention in Example 2 and for the volume overload model in Example 3. As discussed *supra*, applicants have demonstrated both the prevention and treatment of cardiac hypertrophy at this low level of ANP.

Claim 26 has also been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. This rejection is respectfully traversed.

The recitation of the effective amount being 0.025 μg/kg/min is allegedly new matter. According to the Examiner, there is no disclosure of such a dosage used in the treatment of cardiac hypertrophy. As described *supra*, one skilled in the art would recognize that a plasma level of about 0.5 ng/ml is achieved in a human by administration of 0.025 μg/kg/min of the active substance. The statement regarding a "similar dosage" for glucose infusion is not understood, since glucose infusion refers only to the rate of 2.5 μl/min, not dosage.

Claims 6, 8-14, 22, 24 and 26 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled. This rejection is respectfully traversed.

According to the Examiner, the specification enables preventing cardiac hypertrophy in rats using ANP at dosages which do not cause hypertensive or diuretic effect. However, it allegedly does not enable (1) treatment of cardiac hypertrophy in rats

with ANP at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with ANP in species other than rats at dosages which do not cause diuretic and hypotensive effects; (3) treatment of cardiac hypertrophy with agents other than ANP and at dosages which do not cause diuretic and hypotensive effects; and (4) treatment, in any species and with any agent as claimed, at plasma levels and dosages as claimed. The specification allegedly shows only ANP in rats for treatment, and it is not clear whether diuretic and hypotensive effects are not present or how to achieve the effect excluding such mechanisms.

With respect to (1), treatment is indeed shown at dosages which do not cause diuretic and hypotensive effects in Example 2 of the specification.

With respect to (2), the data obtained using rats can be extrapolated to other species. Because the blood level achieved by the dosage used in rats inhibited cardiac hypertrophy without exhibiting diuretic and hypotensive effects, the dosage of 0.025 μg/kg/min in humans will achieve a blood level of about 500 pg/ml without greatly affecting hemodynamics or the amount of urine. The sequence of ANP is highly conserved among the species and the homology of receptors is high. Thus, the data from rats can be extrapolated to other species.

With respect to (3) and (4), one skilled in the art could readily test other substances that act on guanylyl cyclase A natriuretic peptide receptor and find whether and at what dosage cardiac hypertrophy is treated or prevented, but no diuretic or hypotensive effects achieved. No undue experimentation would be necessary for a person skilled in the art.

The studies shown in the application examples could be used, with additional active ingredients being used in place of ANP. Such experimentation would not be "undue."

We note that Knowles et al, *J. Clin. Invest.* 107:975-84 (2001) reported a study using knock-out mice, where it was shown for the first time that the cardiac hypertrophy inhibitory effect and the hypotensive effect of ANP are independent of each other. This later work supports the surprising results obtained by applicants in showing that cardiac hypertrophy could be prevented/treated without diuretic and hypotensive effects.

In view of the above, withdrawal of the rejection is respectfully requested and believed to be in order.

The prior art rejections will now be addressed.

Claims 6 and 8-10 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Blaine et al as evidenced by Espinser. Claims 6, 8 and 9 have also been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Berman et al as evidenced by Espinser. Claims 6 and 8-14 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine or Berman in view of Cao et al. Claims 6 and 11-14 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine or Berman. These rejections are all respectfully traversed.

Blaine describes that ANP was administered for one week to unidentified rat models of cardiac hypertrophy and normal rats, and the water content of the heart (grams H_2O/100 grams tissue) was determined. It describes that ANP inhibited hypertrophy, but indicated only a "reduction in water content." This is entirely different from the results obtained by applicants. In general, cardiac hypertrophy that is considered to cause cardiac failure is

caused by enhanced protein synthesis in cardiac ventricular cells (cell hypertrophy) and collagen production (fibrosis), and not be increases in water content. What was indicated in their Example is considered the same as "control of the volume of body fluids, control of water transfer in and out of the cells" that had already been elucidated for ANP. At the time of Blaine, the diuretic effects of ANP and the effects of transferring water from the tissue were known to those skilled in the art.

By contrast, applicants found the heart weight/body weight ratio, and made clear for the first time that ANP exhibits an inhibitory effect on the weight of the heart *per se*. Also, in clinical trials on humans, applicants have clarified the effectiveness of ANP using two types of models of hypertensive property and volume overload property that are major causes of cardiac hypertrophy. The showing in the instant application that the administration of ANP either before or after the onset of cardiac hypertrophy can reduce cardiac hypertrophy and cause involution has a great clinical significance. This indicates a new direct effect of ANP on the heart that is not based on the previously known diuretic and hypotensive effects of ANP.

Berman describes that since ANP antagonizes the renin-angiotensin-aldosterone system, its derivatives are effective for vasoconstriction, aldosterone secretion, cardiac hypertrophy, etc., in which the renin-angiotensin system is involved. For ANP, it does not have a direct ACE inhibitory effect, but, as a physiological effect, it antagonizes angiotensin II (in vasohypotonic effects, diuretic effects, etc.). It was, and still is, unclear in what signal in the cell it antagonizes angiotensin II and the degree of its antagonistic effect, if any, or whether it has an inhibitory effect of cardiac hypertrophy in *in vivo*

models of cardiac hypertrophy in which hypertrophic stimulation other than by angiotensin II can take part.

In terms of antagonism to angiotensin II, vasodilators such as hydralazine and calcium antagonists indeed antagonize angiotensin II in terms of constriction reactions of blood vessels, but in actual practice, it has been reported that the administration of hydralazine or nifedipin, a calcium antagonist, did not cause inhibition or involution of cardiac hypertrophy though it reduced blood pressure (Linz et al, *Clin. Exp. Hypertens.* 11(7):1325-1350 (1989) or Suzuki et al, *Am. J. Nephrol.* 15(2):129-36 (1995)). Further, since α adrenergic stimulation promotes cardiac hypertrophy α1 blockers are expected to inhibit cardiac hypertrophy. In fact, it has been reported that α1 blockers inhibited the hypertrophy of myocardial cells *in vitro* (*J. Pharm. Pharmacol.* 48(3):323-26 (1996)) by α1 stimulation, prevented the formation of cardiac hypertrophy in rat models of cardiac hypertrophy at pressure overload. However, when it is administered after the formation of cardiac hypertrophy, involution of cardiac hypertrophy was not observed though hypotensive effects were observed (Nishimura et al, *Jpn. Circ. J.* 57(9):893-903 (1993). In fact, while ACE inhibitors have been approved as therapeutic agents for cardiac hypertrophy or cardiac failure, calcium antagonists or α1 blockers have not been used for the treatment of cardiac failure.

Therefore, even if ANP has an effect of antagonizing the angiotensin system, it cannot be expected to involute cardiac hypertrophy at low does that do not adversely affect blood pressure. The therapeutic effect found by applicants, as well as the preventive effect, on cardiac hypertrophy is clinically significant. Such an effect of ANP of treating

(involuting) and preventing cardiac hypertrophy as such dosages is not described in any of the cited references.

Though hypertension is one of the major causes of cardiac hypertrophy, cardiac hypertrophy is formed by a variety of factors such as volume overload, myocardial necrosis by myocardial infarction, etc., genetic mutation of constricting proteins and the like. Except when the underlying disease is hypertension, the blood pressure of patients with cardiac failure is lower than normal and therefore, the fact that it can remove overload to the heart at a dose that does not affect blood pressure and thereby can involute cardiac hypertrophy is very significant tin terms of clinical versatility and significance. Whether such a low dose could antagonize various factors to prevent/treat cardiac hypertrophy, including angiotensin II, could not have been predicted from the report of Cao et al, or from the results of the prior art *in vitro* and *in vivo* data. Applicants finding that an inhibitor could be administered at a dosage of "amount effective for reducing heart weight, wherein said amount is not effective for said diuretic and hypotensive effects" was novel and nonobvious in view of the prior art cited by the Examiner.

With respect to Cao et al, applicants note that ANP at 10^{-6} M was shown to exhibit an inhibitory effect on the growth of about 30% of cardiac fibroblasts. This level is more than 1,000 fold of the blood level of ANP in applicants method.

In view of the above, it is respectfully submitted that none of the cited references either alone or in combination disclose or suggest applicants' claimed methods. Withdrawal of the rejections of record are respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (508) 339-3684 so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: July 25, 2002

Attachment to Reply and Amendment dated July 25, 2002

Marked-up Claims 6 and 22-23

6. (Thrice Amended) A method for treatment of cardiac hypertrophy by reducing heart weight, wherein said reduction of heart weight is not based on diuretic and hypotensive effects, [not based on diuretic and hypotensive effects] comprising continuously administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and is able to accelerate production of cyclic guanosine monophosphate, to a subject in need of such treatment in an amount effective for reducing heart weight, wherein said amount is [and] not effective for said diuretic and hypotensive effects.

22. (Amended) A method for treatment of cardiac hypertrophy by reducing heart weight, wherein said reduction of heart weight is not based on diuretic and hypotensive effects, [not based on diuretic and hypotensive effects] comprising continuously administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and is able to accelerate production of cyclic guanosine monophosphate, to a subject in need of such treatment in an amount effective for reducing heart weight, wherein said amount is [and] not effective for said diuretic and hypotensive effects, wherein said effective amount is an amount sufficient to achieve a plasma level of about 0.5 ng/mL.

23. (Amended) A method for treatment of chronic heart failure by reducing heart weight, wherein said reduction of heart weight is not based on diuretic and hypotensive effects, [not based on diuretic and hypotensive effects] comprising continuously administering a substance that acts on guanylyl cyclase A natriuretic peptide receptor and is able to accelerate production of cyclic guanosine monophosphate to a

Attachment to Reply and Amendment dated July 25, 2002

Marked-up Claims 6 and 22-23

subject in need of such treatment in an amount effective for reducing heart weight, wherein said amount is [and] not effective for said diuretic and hypotensive effects, wherein said effective amount is an amount sufficient to achieve a plasma level of about 0.5 ng/mL.